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Reallocating accelerometer-assessed sedentary time to light or moderate-to-vigorous physical activity reduces frailty levels in older adults: an isothermal substitution approach in the TSHA study

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Running title: Sedentary behavior, physical activity, and frailty in older adults

Abstract

Introduction:

The effects of replacing sedentary time with light or moderate-to-vigorous physical activity on frailty are not well known.

Aim:

To examine the mutually independent associations of sedentary time (ST), light intensity physical activity (LPA) and moderate-to-vigorous intensity physical activity (MVPA) with frailty status in older adults.

Methods:

A total of 628 people aged ≥ 65 years from the Toledo Study of Healthy Aging (TSHA) participated in this cross-sectional study. Frailty was measured using the Frailty Trait Scale. Hip-worn accelerometers were used to capture objective measurements of ST, LPA and MVPA. Linear regression and isothermal substitution analyses were used to examine associations of ST, LPA, and MVPA with frailty status. Analyses were also stratified by comorbidity.

Results:

In single and partition models, LPA and MVPA were negatively associated with frailty. Time in sedentary behavior was not associated with frailty in these models. In the isothermal substitution models, replacing 30 min/day of ST with MVPA was associated with a decrease in frailty (β -2.460; 95% CI: -3.782, -1.139). In contrast, replacing ST with LPA was not associated with favorable effects on this outcome. However, when the models were stratified by comorbidity, replacing ST with MVPA had the greatest effect on frailty in both the comorbidity (β -2.556; 95% CI: -4.451, -0.661) and the no

comorbidity group (β -2.535; 95% CI: -4.343, -0.726). Moreover, the favorable effects of LPA in people with comorbidities was found when replacing 30 min/day of ST with LPA (β -0.568; 95% CI: -1.050, -0.086).

Conclusions:

Substituting ST with MVPA is associated with theoretical positive effects on frailty. People with comorbidity may also benefit from replacing ST with LPA, which may have important clinical implications in order to decrease the levels of physical frailty.

Keywords: accelerometry, sedentary behavior, elderly, aging, exercise, comorbidity.

84 **Introduction**

85 According to Clegg et al. (1), one of the most problematic manifestations of population
86 ageing is the clinical condition of frailty. In Spain, one in two people over 65 years are
87 pre-frail and there is a frailty prevalence of 27.3%, the highest of the 10 European
88 countries tested in the study of Santos-Eggimann et al. (2). Frailty is a multifaceted
89 condition that coincides with a decreased functional reserve capacity in different organ
90 systems. Frailty leads to a number of adverse health outcomes including disability, falls,
91 hospitalization, and death (1). Frailty syndrome increases the need of medical and social
92 care of patients and therefore, increases health-care derived costs. Consequently, the
93 prevention and reduction of frailty is one of the most important challenges that public
94 health authorities face in ageing societies (3).

95 Lifestyle is considered one of the keystones in the development of frailty (4), and
96 increasing physical activity (PA) has been suggested as a fundamental strategy to prevent
97 the onset, perpetuation and progression of this syndrome (5). According to the World
98 Health Organization (6), all older adults over 65 years should accumulate at least 150
99 minutes of moderate intensity aerobic PA, or at least 75 minutes of vigorous intensity
100 aerobic PA, or an equivalent combination of both intensities in 10-minute bouts in order
101 to achieve the health-enhancing benefits of physical activity. However, relatively few
102 adults meet the physical activity guidelines, and the odds of doing so drop as a person
103 ages. Older adults are the most inactive age group, spending 8.7 min/d for males and 5.4
104 min/d for females in objectively measured moderate-to-vigorous physical activity
105 (MVPA) (7).

106 The negative consequences of sedentary behavior, characterized by very low energy
107 expenditure (e.g. sitting or reclining posture) (8), on health have been recently
108 acknowledged (9, 10). Studies in the US and Europe report that older adults spend

between 60 to 80% of their awake time in sedentary behavior which represents 8 to 12 hours per day (11, 12). It has been previously suggested that sedentary time (ST) is associated with frailty in the elderly (13-15) independent of MVPA (16, 17), but in recent international research concerning sedentary time it is necessary to include health results relevant to the geriatric population with the quantification of the dose-response relationship (18).

Recently, light intensity PA (LPA) has been suggested to improve various health outcomes (19). LPA may be more appealing and feasible for currently inactive populations. This is relevant among older adults, where MVPA guidelines are generally not met. Previous research has demonstrated that in inactive older adults and older adults with comorbidities (which tend to be less active and more frail) LPA is associated with better cardiometabolic (19, 20) and mortality outcomes (21). Whether LPA may reduce the frailty level among older adults with comorbidities is still unknown.

In addition, the isothermal substitution approach (22), which has been recently developed, assumes that activity time in a day is finite and that performing one activity involves substitution for another. Depending on the kind of activity that is replaced, the effects on health may be varied. Despite the recently acknowledged impact of sedentary behaviors (13, 15), the potential benefits of replacing sedentary behaviors with LPA or MVPA on frailty among older adults are largely unknown. A deeper understanding on how ST, and PA interact with frailty in older adults is highly relevant to public health professionals for identifying research-informed strategies for prevention and management of frailty in this population group.

Therefore, the aim of this study was to use the isothermal substitution technique to investigate the displacement effect of replacing ST with LPA and MVPA on frailty status among older adults in the Toledo Study for Healthy Aging (TSHA). We hypothesized

134 that replacing ST with MVPA will produce reductions in frailty in both older adults with
135 and without comorbidities and that LPA will only be beneficial in older adults with
136 comorbidities.

Methods

Study Design and Participants

This cross-sectional investigation used baseline data from the TSHA. The complete methodology of the TSHA has been reported elsewhere (23, 24). Briefly, the TSHA is a population prospective cohort study aimed at studying the determinants and consequences of frailty in institutionalized and community-dwelling individuals older than 65 years living in the province of Toledo, Spain. Data were collected in three stages. In the first stage six psychologists conducted computer-assisted interviews face to face with potential subjects. In the second stage, three nurses performed a physical examination followed by clinical and performance tests at the subject's home. In the third stage, the participants went to their health center to provide a blood sample while fasting. At this stage, participants were invited to wear an accelerometer for a week. Only those who agreed to and wore the accelerometer were included in the study (n= 628). Data were collected from June 2006 until September 2009. Signed informed consent was obtained from all participants. The study was approved by the Clinical Research Ethics Committee of the Toledo Hospital.

Measurements

Frailty status

The Frailty Trait Scale (FTS) (25) was used to assess frailty in this study. The FTS includes 7 aspects: energy balance and nutrition, activity, nervous system, vascular system, weakness, endurance, and slowness. These domains become operational through 12 items. Each item score represents a biological trait. Each item ranges from 0 (the best) to 4 (the worst) except in the "chair test" where the range is from 0 to 5 points because of

the necessity of scoring those unable to stand a single time. When appropriate, items are analyzed according to the item's quintile distribution in the population.

To be included in the study, the participants had to overcome at least 75% (9 of the 12) of the items included in the FTS. The total score was calculated by adding all the scores in each item divided by total score for each individual and multiplying by 100, standardizing the measure to a range from 0 (best score) to 100 (worst score), according to the formula $\text{Total score} = (\sum \text{items score} / \text{total score possible by individual}) * 100$.

Physical activity and sedentary behavior assessment

Physical activity and sedentary behavior were objectively assessed by accelerometry (ActiTrainer; ActiGraph, LLC, Fort Walton Beach, FL). All participants were instructed how to wear an accelerometer on the left hip during waking hours. Participants wore the accelerometer for 7 consecutive days and removed it during any bathing or swimming activities. The ActiTrainer device was initialized to collect data using one minute epochs. Non-wear time was defined as periods of at least 60 consecutive minutes of zero counts, with allowance for two minutes of counts between zero and 100 (26). The study included the results from participants with at least four valid days with at least 480 min (8 h) of wear time without excessive counts (i.e. >20,000 counts). Accelerometer counts were used to derive the time spent in each intensity band: sedentary behavior (<100 counts/min), light-intensity physical activity (100–1951 counts/min) and moderate-to-vigorous physical activity (≥ 1952 counts/min) (27). Although there is a lack of consensus on the use of cut-off points to classify the intensity of the activity, the cut-off points used in this study are the most commonly reported in this population group (28), this makes our results comparable to other studies. Minutes

spent in each of these three behaviors were tallied per day and averaged over all available valid days, expressed as proportions of 24 hours.

Anthropometrics and confounding variables

Participants self-reported their age, sex, ethnicity and educational status. Height and weight were measured using standard procedures. BMI was then calculated as weight (kg) divided by height² (m²). Waist and hip circumference were measured using standard procedures (29). Waist-to-hip ratio was then calculated by dividing waist circumference (cm) by hip circumference (cm).

The Charlson Comorbidity Index was used to account for comorbidity status of participants in the study (30). Diseases included in this Index and their weighting are: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes (Weight 1); hemiplegia, moderate or severe kidney disease, diabetes with complication, tumor, leukemia, lymphoma (Weight 2); moderate or severe liver disease (Weight 3); metastatic solid tumor, and AIDS (Weight 6). We also assessed objective cognitive function using the Mini-Mental State Examination (31). Finally, the number of prescription and non-prescription drugs within the Anatomical Therapeutic Chemical (ATC) Classification System taken by the participant was calculated (32).

The Short Physical Performance Battery (SPPB) was used to assess physical function in this study (33). The SPPB measures gait speed (8-foot walk), standing balance, and lower extremity strength and endurance (chair rise task). The tests were performed and scored as described in the original protocol (33).

Statistical analysis

All analyses were performed using the statistical software SPSS version 24.0 (IBM Corp., Armonk, NY). Mean (standard deviation) and frequency (percentage) were provided for continuous and categorical variables, respectively. Descriptive variables were compared between included and excluded participants with an independent t-test or Chi-square test for continuous and categorical variables, respectively. Linear regression models were used to examine associations between time spent (minutes/day) in sedentary behavior, LPA and MVPA with the score in the FTS. Models were adjusted for pre-specified covariates hypothesized to be independently associated with both exposure and outcome variables, including sex, age, educational status, polypharmacy status, functional fitness (SPPB), waist-to-hip ratio, comorbidity status (Charlson Index) and cognitive function (MMSE). Variance inflation factor (VIF) was calculated to quantify the severity of multicollinearity in the regression analyses. All VIF's were below 10. The Condition Number and Durbin–Watson statistic were also analyzed. When performing subgroup analysis by comorbidity status, the Charlson Index was removed from the covariates. Subjects without comorbidity were those who scored 0 and subjects with comorbidity scored 1 or higher on the Charlson Index. Three different linear regression models were used (34). The first set of models are single-factor examining the association of each intensity category (ST, LPA, and MVPA) with frailty status without mutual adjustment for other activity categories. The second are partition models examining the association of each intensity category whilst controlling for each of the other categories of activity. The third are isotemporal substitution models that represent the estimated effects of substituting ST with an equal amount of time spent in LPA or in MVPA. In this model, ST was excluded while total wear time was kept constant in the equation (22). For ease of interpretation, 30-minute units were chosen as time units for each behavior. These

234 models assume linear relationships between dependent and independent variables which
235 were determined prior to performing these analyses.

Results

From the initial sample ($n = 628$), data from 519 participants (male, 45.1%; mean age 78.8 ± 4.6 years) were included in the analysis. Exclusion criteria were: missing frailty data ($n = 27$) or covariates ($n = 17$), and insufficient accelerometer wear time data ($n = 65$). Descriptive variables between those who were included in the analyses versus those who were excluded due to insufficient accelerometer wear time are presented in Table 1. Compared to the included sample, excluded participants were not different in any outcome. For the included sample, participants spent 17.6 minutes per day of the wear time in MVPA and 224 minutes in LPA on average. Sedentary time accounted for 69.5% of the wear time (i.e. 540.0 ± 93.9 minutes).

****Insert Table 1 here****

Table 1. Comparison of characteristics in those included and excluded by accelerometry from the study

Table 1 Legend: Values are means (SD), unless otherwise indicated. BMI: Body mass index; WHR: Waist-to-hip ratio; FTS: Frailty trait scale; SPPB: Short physical performance battery; MMSE: Mini-mental state examination; SB: Sedentary behavior; LPA: Light physical activity; MVPA: Moderate-to-vigorous physical activity; WHO: World health organization.

Table 2 presents single, partition and isothermal substitution models for the associations between specific activity categories and frailty status after the adjustment for potential confounders.

In single and partition models, LPA and MVPA showed an inverse relationship with the frailty score, but no association was found between ST and frailty. In isothermal substitution models, replacing 30 minutes/day of ST with 30 minutes of MVPA was associated with a decrease in the frailty score ($\beta -2.460$; 95% confidence interval (CI): -

3.782, -1.139). However, replacing ST with LPA was not associated with changes in the frailty score.

****Insert Table 2 here****

Table 2. Single Behavior, partition, and isothermal substitution models for frailty (FTS) in elderly people (n=519)

Table 2 Legend: ^aPrior to the regression models, all behavior variables were divided by a constant of 30 so that unit increase in the behavior represented an increase of 30 min/day within the given behavior. Bold indicates statistically significant (* $p < 0.05$, ** $p < 0.01$). Covariates for models included sex, age, educational status, number of drugs, functional fitness (SPPB), waist-to-hip ratio, comorbidity status (Charlson Index) and cognitive function (MMSE). For model 1, sedentary behavior and covariates were entered in the model. For model 2, light physical activity and covariates were entered in the model. For model 3, moderate-to-vigorous physical activity and covariates were entered in the model. For models 4, 5 and 6, sedentary behavior, light physical activity, moderate-to-vigorous physical activity and covariates were entered in the model. For models 7 and 8, light physical activity, moderate-to-vigorous physical activity and covariates (plus total behavior time) were entered in the model (sedentary behavior dropped).

Table 3 displays the results of the single, partition and isothermal substitution models for ST, LPA and MVPA on frailty status divided by comorbidity status. In people without comorbidity, only MVPA was associated with a decrease in the frailty score, as shown by the single and partition models. However, for people with comorbidity LPA showed an inverse relationship with the frailty score, in addition to MVPA. Associations were also observed between increased sedentary time and increased frailty status in the single model in people with comorbidity.

Reallocating 30 minutes/day of ST to 30 minutes of LPA or MVPA in people with comorbidity resulted in an estimated reduction in the FTS (adjusted β -0.568; 95% CI: -1.050, -0.086; adjusted β -2.556; 95% CI: -4.451, -0.661 respectively). Similarly, replacing 30 minutes/day of ST with 30 minutes of MVPA showed a decrease on the

frailty score (adjusted β -2.535; 95% CI: -4.343, -0.726) in people without comorbidity. However, in people categorized as being without comorbidities, the reallocation of 30 minutes/day of ST to 30 minutes of LPA was not associated with significant changes in the frailty score.

******Insert Table 3 here******

Table 3. Single Behavior, partition, and isothermal substitution models for frailty (FTS) subdivided by comorbidity (Charlson Index) in elderly people (n=519)

Table 3 Legend: ^aPrior to the regression models, all behavior variables were divided by a constant of 30 so that unit increase in the behavior represented an increase of 30 min/day within the given behavior. Bold indicates statistically significant (* p <0.05, ** p <0.01). Covariates for models included sex, age, educational status, number of drugs, waist-to-hip ratio, functional fitness (SPPB) and cognitive function (MMSE). For model 1, sedentary behavior and covariates were entered in the model. For model 2, light physical activity and covariates were entered in the model. For model 3, moderate-to-vigorous physical activity and covariates were entered in the model. For models 4, 5 and 6, sedentary behavior, light physical activity, moderate-to-vigorous physical activity and covariates were entered in the model. For models 7 and 8, light physical activity, moderate-to-vigorous physical activity and covariates (plus total behavior time) were entered in the model (sedentary behavior dropped).

Discussion

This study aimed to investigate the relationship between physical activity, sedentary behavior and frailty. We first assessed the association between these factors using a classical approach, then using a theoretical model, to examine how the displacement of activity of different intensities is associated with changes in the frailty score using isotemporal substitution modelling. Our results estimate that replacing 30 minutes of ST with an equivalent amount of MVPA is associated with a more theoretically favorable frailty status in older adults, regardless of comorbidity or physical function status. Equal time-exchange of ST with LPA is predicted to reduce frailty but only in older adults with comorbidity (52.6% in our subsample). In addition, the modelled relationships also suggest potential benefits of LPA in those with comorbid conditions, which may be a more feasible and less challenging approach than more strenuous activity.

In our study, we found that replacing sitting time with MVPA resulted in reductions in the Frailty Trait Scale. This is consistent with previous findings where MVPA was associated with frailty even after controlling for ST (16). MVPA is well known to affect cognitive and physical outcomes, all known to impact frailty. Supporting our results are the findings of Song et al. (17) and Peterson et al. (35) which show evidence that ST negatively impacts on frailty in older adults. Likewise, Fanning et al. (36) only found an improvement in self-regulatory behavior and executive functioning when 30 min of ST was replaced by 30 min of MVPA time.

We have found in single and partition models that LPA has a role on frailty. Some authors have found a positive relationship between LPA and different outcomes regarding frailty, while others have not. Elkins (37) showed that daily time spent in LPA is associated with lower risk of onset and progression of disability whilst Lee et al. (38) found a positive

effect of LPA in cognitive status. Jantunen et al. (39) also showed that LPA was positively associated with better physical performance. However, Pau et al. (40) found that LPA is not the most adequate intensity to improve daily static and dynamic motor tasks.

As a novelty, our grouping analysis shows that only in people reporting comorbidities did LPA bring benefits in terms of frailty. Other studies have shown the beneficial effects of LPA in the isothermal substitution analyses. Ekblom-Bak et al. (41) showed significant lower metabolic syndrome prevalence by replacing 10 minutes of ST with the same amount of LPA. Similarly, Fishman et al. (42) and Schmid et al. (43) found that replacing 30 min of ST with LPA was associated with significant reduction in mortality risk. Our findings show that in frail individuals, with low fitness even minimal movement can positively impact health (44). But when a certain fitness level is reached, more strenuous activity is needed to elicit more beneficial results.

Despite requiring between 4-5 times more LPA to elicit the same changes in frailty compared with MVPA, according to our estimates, the benefits of LPA for improving frailty status in those with comorbidities is of relevance from a public health perspective as might be a population, of those with comorbidities, that cannot or do not find opportunities to (frail older adults spend 84.9% of their daily time in sedentary behaviors (45)) become engaged in MVPA successfully. Thus, replacing ST (e.g., television viewing, sitting) with LPA (e.g., leisure walking, active transport) may be a more feasible strategy to reduce the risk of frailty in older adults with additional disease. Future longitudinal experimental studies should confirm these results.

This study has several strengths and limitations. The sample includes a relatively large number of community-dwelling older adults with objectively assessed frailty and physical activity. However, when comparing the full cohort with the included sample there were differences in most outcomes used in this study so caution should be exercised when

364 interpreting the results. Although there is no established gold standard to identify frailty,
365 the Frailty Trait Scale, derived from the classical model proposed by Fried et al. (46) in
366 combination with the positive aspects of the Frailty Index of Rockwood et al. (47), has
367 been suggested as a more sensitive scale for detecting changes in the individual's
368 biological status (25). The validity of this scale was evaluated by assessing its association
369 with comorbidities, biomarkers associated with frailty status, and by comparing its
370 predictive value for adverse events with the two most frequently used frailty scales:
371 Frailty Phenotype (46) and the Frailty Index (47). Although accelerometry has some
372 advantages over questionnaires and other self-report methods (48), it is not exempt from
373 error. Waist-worn accelerometers are not able to detect differences between sitting and
374 standing positions, and therefore the measurement of ST can be overestimated. In
375 addition, the cut-off points used in this study and the algorithm chosen to discard zero
376 value periods can affect the amount of different physical activity intensity ranges and
377 sedentary behavior.

378 Causal inferences are limited due to the cross-sectional nature of the study. Moreover,
379 isothermal substitution models represent a mathematical way of replacing one behavior
380 with another, so the results should be interpreted with caution. There is therefore a need
381 for more experimental research in this area, especially in the clinical setting, in order to
382 better understand the impact of replacing ST with activity of different intensities on frailty
383 status among older adults. Another limitation of the study may be the non-measurement
384 of sleep, an important behavior that may affect the associations found in this study.

Conclusions

In conclusion, this study demonstrates that replacing 30 min/day of sedentary behavior with the same amount of MVPA could bring benefits in terms of frailty status among older adults. Participants with comorbidities may also benefit from the substitution of ST by LPA. From a public health perspective, this is an important message in order to improve frailty status through increasing LPA, which a priori seems to be a more feasible approach as opposed to increasing MVPA in this population group. Future research should move beyond this hypothetical, observational evidence and identify more-robust indication of the frailty outcomes of experimentally reallocating time spent in sedentary behaviors with physical activities of different intensities (49).

Conflict of interest

None to declare.

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